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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,267	02/07/2007	Gaetano Giammona	1108.1003	4701

20311 7590 09/16/2011

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EXAMINER	
BROWE, DAVID	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
09/16/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/596,267	GIAMMONA ET AL.	
	Examiner	Art Unit	
	DAVID BROWE	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,5-15 and 18-21* is/are pending in the application.

5a) Of the above claim(s) *21* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,5-15 and 18-20* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/GB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

+DETAILED ACTION

This action is in response to Applicant's amendments and arguments in the reply filed June 30, 2011 to the Non-final rejection mailed April 13, 2011. Claims 7, 11-12, 15, and 18 have been amended; claims 2-4 and 16-17 have been cancelled; and claims 20-21 have been newly added. Claims 1, 5-15, and 18-21 are pending in the application.

Withdrawal of Prior Claim Rejections - 35 USC § 112 2nd Paragraph

Claims 7-12 and 15 have been satisfactorily amended to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 16-17 have been cancelled. Therefore, the 35 USC 112 2nd Paragraph rejection of claims 7, 11-13, and 15-19 is hereby withdrawn.

Species Election

A. Claims 1, 5-15, and 18-21 are generic to the following disclosed patentably distinct species: active ingredient. The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to **elect one of the following disclosed active ingredients for prosecution on the merits** to which the claims shall be restricted if no generic claim is finally held to be allowable:

a) an alkanoyl L-carnitine of claim 12

b) a single disclosed active ingredient selected from newly added claim 21

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

B. Newly submitted claim 21 is directed to species of active ingredients that are independent or distinct from those species originally claimed for the following reasons: newly submitted claim 21 is directed to active ingredients other than the alkanoyl L-carnitines disclosed in claim 12

Since Applicants have received an action on the merits for the alkanoyl L-carnitines of claim 12 as the active ingredient, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, newly added claim 21 is hereby withdrawn from consideration as being directed to a non-elected species of the invention. See 37 CFR 1.142(b) and MPIP § 821.03.

Claim Rejections - 35 USC § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of treating ulcerative colitis in a patient, comprising administering the composition of claim 8 to said

patient, does not reasonably provide enablement for treatment of any and all types of diseases, ailments, or other conditions for which treatment may be desired, as broadly claimed.

Claim 15 is directed to a method of treating a patient or an animal in need thereof, but does not specify what is being treated. Therefore, the claim scope expands to any and all types of diseases, ailments, or other conditions for which treatment may be desired. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims without an undue amount of experimentation.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: 1) scope or breadth of the claims; 2) nature of the invention; 3) relative level of skill possessed by one of ordinary skill in the art; 4) state of, or the amount of knowledge in, the prior art; 5) level or degree of predictability, or a lack thereof, in the art; 6) amount of guidance or direction provided by the inventor; 7) presence or absence of working examples; and 8) quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are weighed, it is the Examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) Scope or breadth of the claims

The claims are broader in scope than the enabling disclosure. Since no particular disease, ailment or condition being treated is specified in claim 15, Applicant is effectively purporting to have invented a method of treating any and all diseases, ailments, and conditions for which treatment may be desired. In claim 17, Applicant is purporting to have invented a method to treat any and all cardiovascular diseases, tumors, central and peripheral nervous system diseases, and/or intestinal diseases. However, Applicant in the specification has only demonstrated how to prepare anionic hydrogels loaded with L-carnitine, and that the said hydrogels are capable of releasing L-carnitine at pH 1 and another, unspecified pH. Not a single disease, ailment or other condition has been treated in practice by Applicant's claimed anionic hydrogel composition.

2) Nature of the invention

The nature of the invention is directed to treatment of any and all diseases, ailments, or other conditions for which treatment may be desired comprising administering an anionic hydrogel matrix containing PHEA and one or more active ingredients. The nature of the invention of claim 15 is too broad to be ascertained.

3) Relative level of skill possessed by one of ordinary skill in the art

MPEP 2141.03 states (in part), "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 167 LEd2d 705, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." Id. Office personnel may also take into account "the inferences and

creative steps that a person of ordinary skill in the art would employ." Id. At 1396, 82 USPQ2d at 1396. The "hypothetical person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art." Ex parte Hiyamizu, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (The Board disagreed with the examiner's definition of one of ordinary skill in the art (a doctorate level engineer or scientist working at least 40 hours per week in semiconductor research or development), finding that the hypothetical person is not definable by way of credentials, and that the evidence in the application did not support the conclusion that such a person would require a doctorate or equivalent knowledge in science or engineering.).

4) State of, or the amount of knowledge in, the prior art

Cavazza *et al.* (U.S. Patent No. 6,013,670) disclose a method of treating ulcerative colitis in a patient, comprising administering to the patient an effective amount of a pharmaceutical composition of a lower-alkanoyl L-carnitine ot its pharmaceutically acceptable salt in an oral dosage form, wherein the lower-alkanoyl L-carnitine is preferably Propionyl L-carnitine, butyryl L-carnitine, and their pharmacologically acceptable salts (Col. 1, lns. 6-10, 54-56; Col. 2, lns. 3-9, 15-19). Chang *et al.* (Arch Biochem Biophys. 2002. 405(1): abstract) disclose that L-carnitine can inhibit injury in the kidney and small intestine by the potent anticancer agent, cisplatin; but L-carnitine has no appreciable effect on the tumoricidal action of cisplatin. L-carnitine alone has

never been shown to be an effective treatment agent for colorectal cancer or any other types of tumors or cancers.

5) Level or degree of predictability, or a lack thereof, in the art

Although cancer researchers have made great progress in elucidating fundamental concepts in cancer pathogenesis and development, and have devised a variety of treatment entities and schemes, there is no magic bullet, and no known therapy has been reported to be effective against all cancers. (*Gnewuch and Sosnovsky. 2002. Cell. Mol. Life Sci. 59:959-1023*).

Cancer therapy is very unpredictable. A cancer treatment agent or regimen can be effective against some types of cancer, but not others; and can also be more effective against earlier stages of the same cancer than later stages. For example, 5-FU, a mainstay treatment for colorectal cancer, is ineffective in advanced stages of colorectal carcinoma (*Eisenstaedt et al. 1987. Cancer Treat. Rep. Jul-Aug. 71(7-8):779-780*). Further, when administered systemically, as via an ordinary dosage form, 5-FU is ineffective against brain tumors (*Menei et al. 1996. Neurosurgery, Jul. 39(1): 117-123*).

6) Amount of guidance or direction provided by the inventor

The specification presents guidance on preparing anionic hydrogels containing irradiation-mediated cross-linked PHEA and with L-carnitine incorporated therein. Further, L-carnitine release characteristics from the said hydrogel are illustrated at pH 1.

7) Presence or absence of working examples

The specification completely fails to provide scientific data and working embodiments with respect to treating any type of disease, ailment or other conditions

with the composition of the invention. However, Cavazza *et al.* (U.S. Patent No. 6,013,670) is enabling for treating a particular condition using Applicant's composition of claim 8.

8) Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure

One of skill in the art would have to achieve pioneering and revolutionary breakthroughs in the field of tumor research alone to make and use the claimed invention as an effective therapy against any and all tumor disorders, based on the content of the supporting disclosure. For example, since Applicants are essentially claiming that their anionic hydrogel containing L-carnitine can treat any and all types of tumor disorders when administered, one of ordinary skill in the art would have to devise how to make and use the demonstrated hydrogel, wherein the only active agent is L-carnitine, to treat any and all tumor disorders, when L-carnitine has not previously been shown to display any tumoricidal effect, and other well known antitumor agents cannot treat all tumor types. As a result, one of ordinary skill in the art would be required to conduct an undue amount of experimentation to determine if the method does indeed treat any and all tumors.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections - 35 USC § 103

(Rejections I and II)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

I. **Claims 1, 5-11, 14-15, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bromberg *et al.* (U.S. Patent Application Pub. No. 2003/0152623; published Aug. 14, 2003), in view of Blum *et al.* (U.S. Patent No. 6,294,591; published Sep. 25, 2001), and Giammona *et al.* (*Biochimica et Biophysica Acta 1428(1999): 29-38;* published 1999)**

I. Applicant Claims

Applicants claim an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA), suitably derivatised with insertion of the photo-cross-linkable groups glycidyl methacrylate (GMA) and methacrylic anhydride (MA) in the side chain, in the presence of acid comonomers. The acid comonomer is methacrylic acid or acrylic acid. The irradiation agent is selected from the group consisting of gamma rays, beta rays, and ultraviolet radiation. The matrix is preferably in the form of microparticles; and can also be in the form of nanoparticles, gels, films, cylinders, or sponges.

The matrix can contain one or more active ingredients and pharmaceutically acceptable excipients; and is for oral use. The excipients are selected from the group consisting of bioadhesives, chitosans, polyacrylamides, natural or synthetic rubbers, and acrylic acid polymers. The active ingredient(s) is selected from the group consisting of analgesic agents, antitussive agents, bronchodilators, antipsychotics, antihypertensive agents and coronary dilators, selective 6-2 antagonists, calcium antagonists, anti-Parkinson agents, hormones, non-steroidal and steroidal anti-inflammatory agents, antihistamines, spasmolytics, anxiolytics, antidiabetic agents,

cathartics, anti-epileptic agents, anti-cancer agents, disinfectants, sodium fluoride, cardioactive agents, and L-carnitine and/or alkanoyl L-carnitine or a pharmaceutically acceptable salt thereof.

Applicants further claim a method of treating a patient or an animal in need thereof with the matrix composition, administered by the parenteral or vaginal routes, for the treatment of cardiovascular, nervous system, intestinal and tumor diseases.

I. Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Bromberg *et al.* disclose an anionic hydrogel matrix obtained by cross-linking of polymers (Pg. 2, sec. 0012; Pg. 3, sec. 0013-0014; Pg. 4, sec. 0038; Pg. 5, secs. 0049-0052; limitations of claim 1). The polymer is any polyaspartamide, which would encompass the specific polyaspartamide, α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA) (Pg. 5, secs. 0050, 0052; limitation of claim 1). The matrix is preferably in the form of microparticles (Pg. 25, sec. 0193, limitation of claim 7)

The matrix can contain one or more active ingredients and pharmaceutically acceptable excipients; and is for oral use (Pg. 4, sec. 0039; Pg. 21, secs. 0137, 0144; Pg. 22, secs. 0145, 0147-0149, 0152-0154; Pg. 23, secs. 0171, 0180; Pg. 24, secs. 0182-0183; limitations of claims 8-11, and 14). The excipients are selected from the group consisting of bioadhesives, chitosans, polyacrylamides, natural or synthetic rubbers, and acrylic acid polymers (Pg. 23, sec. 0180, limitations of claim 10). The active ingredient(s) is selected from the group consisting of analgesic agents, antitussive agents, bronchodilators, antipsychotics, antihypertensive agents and coronary dilators, selective 6-2 antagonists, calcium antagonists, anti-Parkinson agents,

hormones, non-steroidal and steroidal anti-inflammatory agents, antihistamines, spasmolytics, anxiolytics, antidiabetic agents, cathartics, anti-epileptic agents, anti-cancer agents, disinfectants, sodium fluoride, cardioactive agents, and L-carnitine and/or alkanoyl L-carnitine or a pharmaceutically acceptable salt thereof (Pg. 21, secs. 0137, 0144; Pg. 22, secs. 0145, 0147-0149, 0152-0154; Pg. 23, secs. 0171, limitations of claim 11).

Bromberg *et al.* further disclose a method of treating a patient or an animal in need thereof with the matrix composition; administered by the parenteral or vaginal routes, for the treatment of cardiovascular, nervous system, intestinal and tumor diseases (Pg. 20, secs. 0134-0135; Pg. 21, secs. 0136, 0139-0142, 0144; Pg. 24, sec. 0184-0185, limitations of claims 15, 17, 19).

Blum *et al.* disclose an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of acrylate or methacrylate copolymers, derivatised with photo-cross-linkable groups, in the presence of acid comonomers (Col. 1, lns. 6-7, 12-18, 53-56, 63-67; Col. 2, lns. 1-3, 30-34; Col. 3, lns. 66-67; Col. 4, lns. 1-10, 22-23, 50-51, limitations of claims 1-3). The photo-cross-linkable groups are derived from the insertion of glycidyl methacrylate (GMA) and methacrylic anhydride (MA) in the side chain of the polymers; the acid comonomer is methacrylic acid or acrylic acid (Col. 3, lns. 66-67; Col. 4, lns. 1-10, limitations of claim 1-2). The irradiation agent is selected from the group consisting of gamma rays, beta rays, and ultraviolet radiation (Col. 2, lns. 4-13, limitations of claims 1, 3).

Giammona *et al.* disclose an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA) polymers, derivatised with photo-cross-linkable groups. The photo-cross-linkable groups are derived from the insertion of glycidyl methacrylate (GMA) in the side chain of the polymers; and the irradiation agent is selected from the group consisting of gamma rays, beta rays, and ultraviolet radiation (limitations of claims 1-3).

I. Ascertainment of the Difference Between the Scope of the Prior Art and the Claims (MPEP §2141.012)

Bromberg *et al.*, while disclosing an anionic hydrogel matrix made by cross-linking polyaspartamide polymers, do not explicitly disclose that the specific polyaspartamide polymer is α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA), derivatised by insertion of glycidyl methacrylate (GMA) or methacrylic anhydride (MA); and that the cross-linking of polymers is achieved by beta-, gamma-, or UV-irradiation in the presence of acid comonomers.

I. Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the present invention to combine the respective teachings of Bromberg *et al.*, Blum *et al.*, and Giammona *et al.*, outlined *supra*, to devise applicants claimed invention. Cross-linked polymer matrix synthesis traditionally required the use of toxic initiators and contaminating chemical cross-linking agents, often used unwanted or unpleasant solvent systems, and required additional laborious purification steps (Blum

et al., Col. 1, lns. 18-52; Giammona *et al.*); an approach not optimal for preparing products intended for medical or veterinary use. A skilled artisan, therefore, would be motivated to synthesize a stimulus-responsive, cross-linked polyaspartamide hydrogel matrix, as taught by Bromberg *et al.*; with the clean, safe, and effective irradiation-mediated cross-linking approach via insertion of GMA and MA groups and use of acid comonomers, as taught by Blum *et al.*; using a particular polymer, such as PHEA, that is nontoxic, resistant to damage from radiation, and that has previously been shown to be cross-linkable by insertion of GMA, as taught by Giammona *et al.*; with the reasonable expectation that this approach will successfully produce a clean, safe and effective drug delivery vehicle for use in the medical and veterinary fields, with less effort and toxic contamination, as shown previously (Blum *et al.*; Giammona *et al.*).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

II. **Claims 1, 8, 11-13, 15, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bromberg *et al.* (U.S. Patent Application Pub. No.**

2003/0152623; published Aug. 14, 2003), in view of Blum *et al.* (U.S. Patent No. 6,294,591; published Sep. 25, 2001), Giammona *et al.* (*Biochimica et Biophysica Acta 1428(1999): 29-38;* published 1999), and Cavazza (U.S. Patent No. 6,013,670; published Jan. 11, 2000).

II. Applicant Claims

Applicants claim an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA), suitably derivatised with insertion of the photo-cross-linkable groups glycidyl methacrylate (GMA) and methacrylic anhydride (MA) in the side chain, in the presence of acid comonomers. The acid comonomer is methacrylic acid or acrylic acid. The irradiation agent is selected from the group consisting of gamma rays, beta rays, and ultraviolet radiation. The matrix is preferably in the form of microparticles; and can also be in the form of nanoparticles, gels, films, cylinders, or sponges.

The matrix can contain one or more active ingredients and pharmaceutically acceptable excipients; and is for oral use. The excipients are selected from the group consisting of bioadhesives, chitosans, polyacrylamides, natural or synthetic rubbers, and acrylic acid polymers. The active ingredient(s) is selected from the group consisting of analgesic agents, antitussive agents, bronchodilators, antipsychotics, antihypertensive agents and coronary dilators, selective 6-2 antagonists, calcium antagonists, anti-Parkinson agents, hormones, non-steroidal and steroidal anti-inflammatory agents, antihistamines, spasmolytics, anxiolytics, antidiabetic agents, cathartics, anti-epileptic agents, anti-cancer agents, disinfectants, sodium fluoride,

cardioactive agents, and L-carnitine and/or alkanoyl L-carnitine or a pharmaceutically acceptable salt thereof. The alkanoyl L-carnitine is selected from the group consisting of acetyl, propionyl, butyryl, valeryl, and isovaleryl L-carnitine.

Applicants further claim a method of treating a patient or an animal in need thereof with the matrix composition, administered by the parenteral or vaginal routes, for the treatment of cardiovascular, nervous system, intestinal and tumor diseases, wherein the intestinal disease is chronic ulcerative colitis or Crohn's disease, and the drug useful for the treatment of chronic intestinal disease is propionyl L-carnitine.

II. Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Bromberg *et al.* disclose an anionic hydrogel matrix obtained by cross-linking of polymers (Pg. 2, sec. 0012; Pg. 3, sec. 0013-0014; Pg. 4, sec. 0038; Pg. 5, secs. 0049-0052; limitations of claim 1). The polymer is any polyaspartamide, which would encompass the specific polyaspartamide, α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA) (Pg. 5, secs. 0050, 0052; limitation of claim 1). The matrix is preferably in the form of microparticles (Pg. 25, sec. 0193, limitation of claim 7)

The matrix can contain one or more active ingredients and pharmaceutically acceptable excipients; and is for oral use (Pg. 4, sec. 0039; Pg. 21, secs. 0137, 0144; Pg. 22, secs. 0145, 0147-0149, 0152-0154; Pg. 23, secs. 0171, 0180; Pg. 24, secs. 0182-0183; limitations of claims 8-11, and 14). The excipients are selected from the group consisting of bioadhesives, chitosans, polyacrylamides, natural or synthetic rubbers, and acrylic acid polymers (Pg. 23, sec. 0180, limitations of claim 10). The active ingredient(s) is selected from the group consisting of analgesic agents,

antitussive agents, bronchodilators, antipsychotics, antihypertensive agents and coronary dilators, selective 6-2 antagonists, calcium antagonists, anti-Parkinson agents, hormones, non-steroidal and steroidal anti-inflammatory agents, antihistamines, spasmolytics, anxiolytics, antidiabetic agents, cathartics, anti-epileptic agents, anti-cancer agents, disinfectants, sodium fluoride, cardioactive agents, and L-carnitine and/or alkanoyl L-carnitine or a pharmaceutically acceptable salt thereof (Pg. 21, secs. 0137, 0144; Pg. 22, secs. 0145, 0147-0149, 0152-0154; Pg. 23, secs. 0171, limitations of claim 11).

Bromberg *et al.* further disclose a method of treating a patient or an animal in need thereof with the matrix composition; administered by the parenteral or vaginal routes, for the treatment of cardiovascular, nervous system, intestinal and tumor diseases (Pg. 20, secs. 0134-0135; Pg. 21, secs. 0136, 0139-0142, 0144; Pg. 24, sec. 0184-0185, limitations of claims 15, 17, 19).

Blum *et al.* disclose an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of acrylate or methacrylate copolymers, derivatised with photo-cross-linkable groups, in the presence of acid comonomers (Col. 1, lns. 6-7, 12-18, 53-56, 63-67; Col. 2, lns. 1-3, 30-34; Col. 3, lns. 66-67; Col. 4, lns. 1-10, 22-23, 50-51, limitations of claims 1-3). The photo-cross-linkable groups are derived from the insertion of glycidyl methacrylate (GMA) and methacrylic anhydride (MA) in the side chain of the polymers; the acid comonomer is methacrylic acid or acrylic acid (Col. 3, lns. 66-67; Col. 4, lns. 1-10, limitations of claim 1-2). The irradiation agent is selected from the group consisting

of gamma rays, beta rays, and ultraviolet radiation (Col. 2, lns. 4-13, limitations of claims 1, 3).

Giammona *et al.* disclose an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA) polymers, derivatised with photo-cross-linkable groups. The photo-cross-linkable groups are derived from the insertion of glycidyl methacrylate (GMA) in the side chain of the polymers; and the irradiation agent is selected from the group consisting of gamma rays, beta rays, and ultraviolet radiation (limitations of claims 1-3).

Cavazza discloses the therapeutic use of alkanoyl L-carnitines and their pharmaceutically acceptable salts thereof in compositions for the treatment of ulcerative colitis (Col. 1, lns. 5-10, 54-56; Col. 2, lns. 2-9, 15-20, limitations of claims 15, 17-18). The alkanoyl L-carnitine is selected from the group consisting of acetyl, propionyl, butyryl, valeryl, and isovaleryl L-carnitine; the preferred alkanoyl L-carnitine is propionyl L-carnitine (Col. 2, lns. 2-9, limitation of claim 18).

II. Ascertainment of the Difference Between the Scope of the Prior Art and the Claims (MPEP §2141.012)

Bromberg *et al.*, while disclosing an anionic hydrogel matrix made by cross-linking polyaspartamide polymers, do not explicitly disclose that the specific polyaspartamide polymer is α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA), derivatised by insertion of glycidyl methacrylate (GMA) or methacrylic anhydride (MA); and that the cross-linking of polymers is achieved by beta-, gamma-, or UV-irradiation in the presence of acid comonomers. Further, Bromberg *et al.*, while disclosing that the

matrix can contain active agents and be administered for the treatment of disease, do not explicitly disclose that the specific active agent is propionyl L-carnitine; and that the matrix is administered specifically for the treatment of ulcerative colitis. These deficiencies are cured by the teachings of Blum *et al.*, Giammona *et al.*, and Cavazza.

II. Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the present invention to combine the respective teachings of Bromberg *et al.*, Blum *et al.*, and Giammona *et al.* for the reasons provided *supra*. Further, since Bromberg *et al.* disclose that an anionic hydrogel matrix obtained by cross-linking of polyaspartamide polymers can contain a therapeutic agent or a pharmaceutically acceptable salt thereof, and be administered to a patient for the treatment of intestinal diseases, and since Cavazza teaches that propionyl L-carnitine or its pharmaceutically acceptable salt can be administered to a patient in a composition for the treatment of ulcerative colitis, one of ordinary skill in the art would be motivated to insert propionyl L-carnitine or its pharmaceutically acceptable salt into the cross-linked anionic hydrogel matrix of Bromberg *et al.* with the reasonable expectation that this composition would successfully treat ulcerative colitis when administered to a patient in need thereof.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments/remarks filed June 30, 2011 have been fully considered but they are not persuasive.

The Bromberg *et al.* disclosure provides that the following were already known in the art at the time of the present application: *i)* an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of polyaspartamide and/or other suitable polymers, *ii)* anionic hydrogel matrices in the form of microparticles, and *iii)* an anionic hydrogel matrix incorporating active agents and excipients which are administered to a patient or animal by oral, parenteral or vaginal routes for the treatment of intestinal and other types of diseases. It would have been obvious to one of ordinary skill in the art within the meaning of 35 U.S.C. §103, based on the disclosure of Bromberg *et al.* and further employing the combination of the respective teachings of Blum *et al.*, Giammona *et al.*, and Cavazza, already discussed in detail above, to formulate an anionic hydrogel matrix obtained by irradiation-mediated cross-linking specifically of *PHEA derivatized by GMA and MA with acid comonomers* as the particular, suitably derivatized polyaspartamide polymer, and incorporating *propionyl L-carnitine or its pharmaceutically acceptable salt* as the specific active agent, which are administered to a patient or animal by oral,

parenteral or vaginal routes for the treatment of *ulcerative colitis* as the specific intestinal disease.

i) Applicants contend, however, that *Bromberg does not provide for PHEA polymers derivatised by insertion of GMA or MA in the presence of acid comonomers.*

While the Examiner agrees that Bromberg *et al.* do not explicitly disclose an anionic hydrogel matrix comprising specifically PHEA polymers derivatised by insertion of GMA or MA in the presence of acid comonomers; the disclosure of Bromberg *et al.* , that anionic hydrogels can be made from irradiation-mediated cross-linking of polyaspartamide; together with the respective teachings of Giammona *et al.* (the particular polyaspartamide PHEA derivatized with GMA for irradiation-mediated crosslinking to produce anionic hydrogels) and Blum *et al.* (polymer derivitization with GMA as well as MA with acid comonomers for irradiation-mediated cross-linking) outlined *supra* render this limitation obvious within the meaning of 35 USC § 103.

ii) Applicants contend that Blum *et al. does not add anything to the deficiencies of Bromberg….is completely silent with regard to PHEA….is not an analogous prior art....and is not a reference reasonably pertinent to applicants endeavor because logically it does not command itself to an inventor's attention.* Applicants further note that Blum *et al.* discloses *preparing radiation crosslinkable polymers suitable for coatings, paints, adhesives, etc.*.

The Examiner maintains, contrary to applicants assertions, that Blum *et al.* is not only a pertinent reference, it is a key reference the teachings of which disclose the very heart of applicants invention. This position is supported by the following points:

a) Blum *et al.* disclose a general process for preparing radiation cross-linkable polymers in a clean, safe, and effective manner for use in compositions; the very heart of applicants research work is concerned with producing safe and effective cross-linked polymer hydrogel matrices that can be used to deliver active pharmaceutical agents to patients and animals for medical/veterinary treatment of disease.

b) Blum *et al.* disclose a process of preparing (meth)acrylic acid/(meth)acrylate copolymers for irradiation-mediated cross-linking by insertion of GMA and MA groups in the side chains in the presence of acid comonomers; and further disclose using these polymers with suitable agents and excipients in compositions. Preparing polymers for irradiation-mediated cross-linking in this manner, and employing the thus cross-linked polymers in compositions with suitable agents and excipients corresponds with what applicants are claiming as their invention. The Blum *et al.* teachings are further pertinent to applicants endeavor for the following reasons: *i)* (meth)acrylic acid/(meth)acrylate polymers and copolymers are routinely employed in the pharmaceutical and medical arts, particularly in drug delivery vehicles; *ii)* applicants provide for the inclusion of acrylic acid polymers in their composition (claim 10); and *iii)* applicants have previously disclosed a process for preparing PHEA for irradiation-induced cross-linking by the insertion of GMA groups into the side chains, and preparing an anionic hydrogel matrix by irradiation-mediated cross-linking of the modified PHEA polymers.

c) The Blum *et al.* Patent is assigned to BASF Coatings AG. Its no surprise, therefore, that Blum *et al.* would suggest the best mode for the use of their photo-crosslinkable (meth)acrylate copolymers would be in coatings, paints, and surface

adhesives. However, Blum *et al.* further note that their invention is not limited to use in coatings, paints, and surface adhesives; that their invention can be employed in any envisaged application, and that "*the selection of monomers for combination is made in accordance with principles familiar to the skilled worker, such that they satisfy the requirements of the envisaged application*", and that "*these requirements may differ greatly*". A person of ordinary skill in the pharmaceutical arts would thus readily recognize and be able to take advantage of the relevant teachings the Blum *et al.* reference affords to the pharmaceutical arts.

Thus, while *Blum is completely silent with regard to PHEA*, Blum *et al.* adds immensely to the deficiencies of Bromberg *et al.* by disclosing the process for preparing irradiation-crosslinkable polymers by suitably derivatising the polymers by insertion of GMA and MA into the side chains in the presence of acid comonomers, and that these acid comonomers are selected from methacrylic acid and acrylic acid.

Giammona *et al.* disclose the process of preparing irradiation-crosslinkable PHEA by insertion of GMA into the side chain, and preparing irradiation cross-linked hydrogel matrices from said modified PHEA. Applicants assert, however, that *Giammona is completely silent with regard to acid comonomers and methacrylic anhydride (MA).* The Examiner contends, however, that it was already established and disclosed at the time of the present application that PHEA can be photo-crosslinked by insertion of GMA into the side chain, and thus any person of ordinary skill in the art would find it obvious from the disclosure of Blum *et al.* that MA can be inserted as well,

and, further, that the photo-crosslinking reaction can advantageously proceed in the presence of acid comonomers.

iii) Applicants further assert that *Cavazza is irrelevant*, and *only provides for the treatment of chronic inflammatory bowel diseases with lower alkanoyl L-carnitines.*

The Examiner, however, cannot agree that Cavazza is irrelevant. Since applicants claim a method of treating bowel diseases by administering alkanoyl L-carnitines, its obvious from the disclosure of Cavazza that this aspect of applicants invention is already known and is not patentable.

Therefore, for the aforementioned reasons, the 35 U.S.C. § 103 rejections of claims 1, 5-15, and 18-19, of record, are hereby maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID BROWE whose telephone number is (571)270-1320. The examiner can normally be reached on Monday-Friday 8:30AM-6PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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